

**REMARKS**

**I. Claim Status**

Claims 11-16 are pending. Applicants have amended claim 11 to define variables K and v. Support for these amendments can be found on pages 14 and 16 of the published International Patent Application No. WO 2005/090284, which corresponds to the instant application. Applicants have amended claims 14-16 herein in order to place them in proper U.S. claim format. Accordingly, no new matter has been added.

**II. Rejections Under 35 U.S.C. § 112, ¶ 2 and § 101**

The Examiner rejects claims 14-16 under 35 U.S.C. § 112, ¶ 2, as being indefinite for being “use” claims, and under 35 U.S.C. § 101, for failing to fall within any of the defined statutory classes of patentable subject matter. June 15, 2009, Office Action at 3. The Examiner also rejects claim 15 under § 101 “because the claimed recitation of a use, without setting forth any steps involved in a purported method/process, results in an improper definition of a process.” *Id.* at 4.

Applicants have amended claims 14-16 in order to place them in proper U.S. claim format. Specifically, claims 14-16 are amended herein to recite methods of treatment. Thus, Applicants respectfully submit that the rejections are rendered moot by these amendments and should be withdrawn.

**III. Claim Objections**

The Examiner objects to claims 14-16 for depending from cancelled claim 1. June 15, 2009, Office Action at 4. Applicants have amended claims 14-16 so that they depend from pending claim 11. Thus, Applicants respectfully submit that the rejection is rendered moot by this amendment and should be withdrawn.

**IV. Additional Rejections Under 35 U.S.C. § 112, ¶ 2**

The Examiner also rejects claims 11-16 under 35 U.S.C. § 112, ¶ 2, as being indefinite because it is allegedly “unclear whether or not K in the thiophen group is K or S in the Y’ definition below for the compound of formula C or D.” June 15, 2009, Office Action at 5. The Examiner also argues that “the claims contain so many options, variables, possible permutations and different possibilities of attachment of the different options that lack of clarity because the metes and bounds of the claims can not be determined.” *Id.* For example, the Examiner argues that “there is no definition for CO<sub>2</sub>Aryl in the specification.” *Id.*

Applicants respectfully traverse.

Applicants have amended claim 11 to recite that K is S or O, and, thus, the rejection is rendered moot and should be withdrawn.

With respect to CO<sub>2</sub>Aryl, the specification provides a definition of “aryl” on page 19 of published International Patent Application No. WO 2005/090284, which corresponds to this application. Specifically, “aryl” is described and examples, such as phenyl and naphthyl, are disclosed. Therefore, one of ordinary skill in the art would readily understand that CO<sub>2</sub>Aryl means a carboxylic group connected to an aryl group. Thus, Applicants respectfully submit that the rejection is improper and should be withdrawn.

**V. Rejection Under 35 U.S.C. § 112, ¶ 1**

The Examiner rejects claim 15 under 35 U.S.C. § 112, ¶ 1, because it is allegedly not enabling for the prophylaxis of inflammatory disorders. June 15, 2009, Office Action at 6.

Applicants respectfully traverse this rejection for the following reasons.

Examination of the following *In re Wands* factors supports a conclusion that the claim is enabled.

**A. The Nature of the Invention**

The Examiner argues that no definition of “prophylaxis” is provided, and, therefore, “[t]his term is taken in its plain meaning as preventing.” June 15, 2009, Office Action at 6.

Applicants submit that one of ordinary skill in the art would understand, in the context and disclosure of the instant invention, that “prophylaxis” encompasses two types of prophylaxis/prevention. First, prophylaxis means providing a compound of the instant invention to a healthy person who is at risk of becoming ill with a claimed disorder. Second, prophylaxis also means providing a compound of the instant invention to a person who was formerly ill with a claimed disorder, is now successfully cured, in order to prevent a new outbreak of this claimed disorder.

**B. The State of the Prior Art**

The Examiner notes that the Merck manual “teach[es] that inflammatory [diseases] such as Crohn’s disease has no cure, but can be treated with certain drugs to relieve symptoms,” and while “these drugs and surgery can help prevent recurrences,” they do “not prevent[] the disease.” June 15, 2009, Office Action at 6.

Applicants respectfully submit that the Merck manual is concerned with commercial drug compounds and not new developments in medicine, such as the compounds of the instant invention. Prophylaxis of a specific inflammatory disease is

certainly possible by using new drug compounds, as demonstrated by administration of compounds of the instant invention.

**C. The Level of One of Ordinary Skill**

The Examiner states that “[t]he relative skill in those in the art is high,” and “[t]he artisan using Applicant’s invention would generally be a physician with a M.D. degree and several years of experience.” June 15, 2009, Office Action at 7.

Applicants submit that the one of skill in the art would readily understand how to make and use compounds of the instant invention based upon the disclosure, for the reasons discussed below.

**D. The Level of Predictability in the Art**

The Examiner states that “[t]he state of the prior art recognizes that the treatment, but not prevention of inflammatory disorders using different drugs and the lack of guidance in the specification remains highly unpredictable.” June 15, 2009, Office Action at 7.

Applicants note that page 3 of the specification states that “the inhibition of selectin-mediated cell adhesion offers a promising possibility to interfere with and stop the inflammation cascade at a very early step,” and pages 62-66 of the specification provide routine testing protocols to determine whether a compound falling within the scope of the invention can be used to inhibit the binding of P-selectin, L-selectin, or E-selectin to sLe<sup>x</sup> or sLe<sup>a</sup> and tyrosinesulfate residues. Therefore, one of ordinary skill in the art would be able to determine whether a specific compound falling within the scope of the invention has selectin inhibitor activity, which may be used to interfere and stop “the inflammation cascade at a very early step.”

**E. The Breadth of the Claims**

The Examiner states that “[t]he breadth of the claims is that the instant compound for preparing a medicament for the prophylaxis of inflammatory disorders,” and, therefore, “the claims taken together with the specification imply these compounds will prevent inflammatory disorders.” June 15, 2009, Office Action at 7.

Applicants note that page 61 of the specification, for example, discloses a number of different trihydroxy phenyl compounds of the instant invention that Applicants prepared and tested. For various trihydroxy phenyl compounds, pages 62-66 of the specification disclose test results in various individual models, which demonstrate an improvement of the selectin inhibitor activity. Therefore, the scope of the claims is appropriate and commensurate with the disclosure in the specification.

**F. The Amount of Direction Provided By the Inventor, the Existence of Working Examples, and the Quantity of Experimentation Needed to Make or Use the Invention Based on the Content of the Disclosure**

The Examiner states that the “specification has no working examples demonstrating prevention of inflammatory disorders nor do they provide any guidance demonstrating how one of skill in the art would prevent a disease that heretofore was previously unrecognized by those of skill in the art to be able to prevent.” June 15, 2009, Office Action at 7.

Contrary to the Examiner’s allegations, as discussed above, page 61 of the specification, for example, discloses a number of different trihydroxy phenyl compounds of the instant invention that Applicants prepared and tested. For various trihydroxy phenyl compounds, pages 62-66 of the specification disclose test results in various individual models, which demonstrate an improvement of the selectin inhibitor activity.

Therefore, the specification provides the activity for a number of compounds falling within the scope of the invention, and also provides a routine test that one of ordinary skill in the art could use to easily identify other compounds falling within the scope of the invention that also possess selectin inhibitor activity.

For all the aforementioned reasons, Applicants respectfully submit that one of ordinary skill in the art would be able to make and use the claimed invention without undue experimentation. Thus, Applicants respectfully submit that the rejection is in error and should be withdrawn.

**VI. Rejections Under 35 U.S.C. § 103(a)**

The Examiner rejects claims 11, 12, and 14-16 under 35 U.S.C. § 103(a) as unpatentable over Blaakmeer et al., "Structure-Activity Relationship of Isolated Avenanthramide Alkaloids and Synthesized Related Compounds as Oviposition Deterrents for *Piers Brassicae*," Journal of Natural Products, 57(8):1145-51 (1994) ("Blaakmeer") in view of Appeldoorn et al., "Rational Optimization of a Short Human P-selectin-binding Peptide Leads to Nanomolar Affinity Antagonists," Journal of Biological Chemistry, 278(12):10201-207 (2003) ("Appeldoorn"), and Patani et al., "Bioisosterism: A Rational Approach in Drug Design," Chem. Rev., 96:3147-76 (1996) ("Patani"), for the reasons set forth on pages 8-11 of the June 26, 2009, Office Action.

Applicants respectfully traverse this rejection for the following reasons.

With respect to obviousness, several basic factual inquiries must be made in order to determine the obviousness or non-obviousness of claims under 35 U.S.C. § 103. These factual inquiries, set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17, 148 U.S.P.Q. 459, 467 (1966), require the Examiner to:

- (1) Determine the scope and content of the prior art;
- (2) Ascertain the differences between the prior art and the claims in issue;
- (3) Resolve the level of ordinary skill in the pertinent art; and
- (4) Evaluate evidence of secondary considerations.

The obviousness or nonobviousness of the claimed invention is then evaluated in view of the results of these inquiries. *Graham*, 383 U.S. at 17-18, 148 U.S.P.Q. at 467; see also *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1730, 82 U.S.P.Q.2d 1385, 1388 (2007).

Indeed, to establish a *prima facie* case of obviousness, the Examiner must:

make a determination whether the claimed invention “as a whole” would have been obvious at that time to that person. Knowledge of applicant’s disclosure must be put aside in reaching this determination, yet kept in mind in order to determine the “differences,” conduct the search and evaluate the “subject matter as a whole” of the invention.

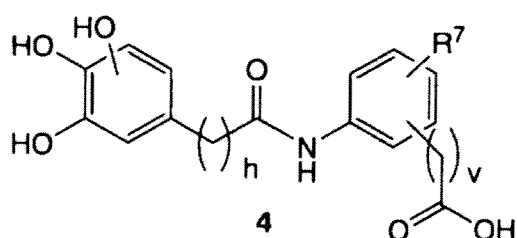
M.P.E.P. § 2142. “The key to supporting any rejection under 35 U.S.C. § 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious.”

*Id.* It is important to note, moreover, that the prior art references relied upon in a rejection “must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed invention.” M.P.E.P. § 2141.03(VI); see also *Graham*, 383 U.S. at 17, 148 U.S.P.Q. at 467.

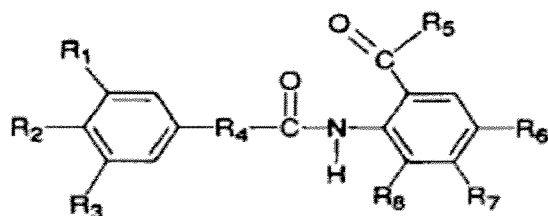
The Examiner has not established a *prima facie* case of obviousness because the claimed invention as a whole would not have been obvious in view of Blaakmeer, Appledoorn, and Patani when considered as a whole. Specifically, Blaakmeer discloses compounds that do not read on the claimed compounds, and one of ordinary skill in the art would not have been motivated to modify the compounds disclosed in

Blaakmeer such that they would read on the claimed compounds. Moreover, even assuming for the sake of argument that one of ordinary skill in the art would have been motivated to modify the compounds of Blaakmeer such that they read on the claimed compounds, which Applicants do not concede, Appeldoorn would not have motivated one of ordinary skill in the art to use the modified compounds to treat, diagnose, or prevent the claimed disorders.

The Examiner notes that the instant application recites, *inter alia*, a pharmaceutical composition comprising at least one compound of the formula C or D, and discloses compound (4):



wherein  $v$  is 2,  $R^7$  is H and both substituents can be located anywhere on the ring. June 26, 2009, Office Action at 9. The Examiner concludes that Blaakmeer discloses the following compound, which reads on the disclosed compound (4):

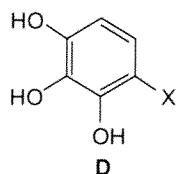
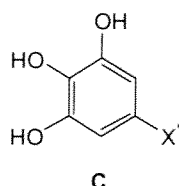


wherein  $R_1$ ,  $R_2$ , and  $R_3$  are OH,  $R_4$  is  $CH_2=CH_2$ ,  $R_5$  is OH,  $R_6$  is OH,  $R_7$  is H, and  $R_8$  is OH. See *id.* (citing compound 10 of Blaakmeer).

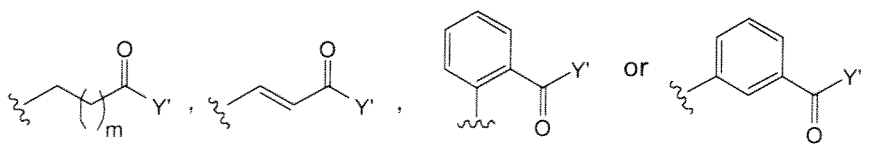


Applicants' specification states that disclosed compound (4) "may be generally applied to all other Y-H building blocks leading to compounds of type (A1), (A2), (B1), and (B2)" as defined in the specification. See Specification at page 26. Thus, disclosed compound (4) can be used to make the claimed compounds. However, there are significant structural differences between compound 10 of Blaakmeer and the claimed compounds, which the Examiner must focus on for his obviousness analysis, rather than merely on disclosed compound (4) that can be used to make the claimed compounds.

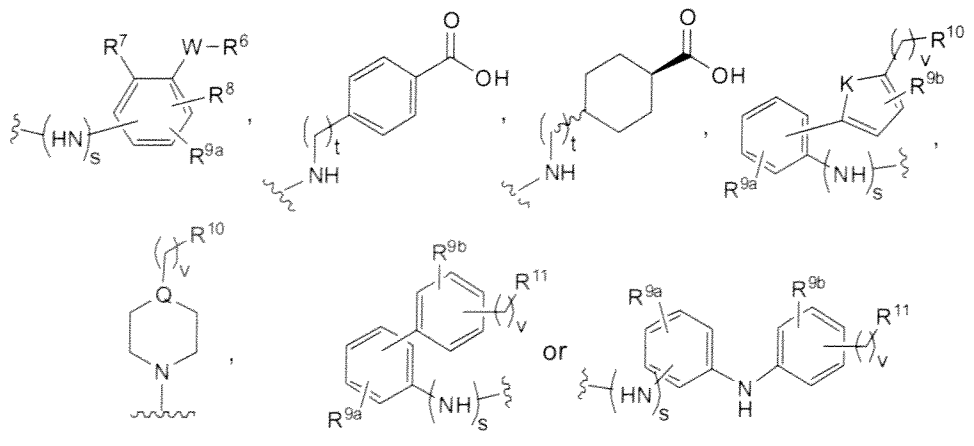
Indeed, the claims recite, *inter alia*, a pharmaceutical composition comprising at least one compound of formula (C) or (D)



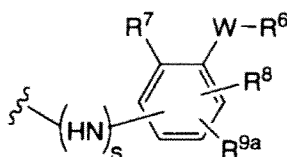
wherein -X' is



Y' is



and the various substituents and variables are as defined in the claims. As is readily apparent upon consideration of variable Y', the amine-part of the structure of the claimed compound is quite different than that disclosed in compound 10 of Blaakmeer. Specifically, in all compounds of Blaakmeer, including compound 10, the aromatic amine part of the molecule has a carboxylic group in ortho-position to the amino group of the phenyl ring. Furthermore, the aromatic amine part of the compounds disclosed in Blaakmeer comprises at least two hydroxy or methoxy groups. In stark contrast to compound 10 of Blaakmeer, if the claimed compound is chosen to have the following Y' substituent, for example:



the carboxylic group (i.e., W is  $-(CH_2)_v$ , v is 0, and R<sup>6</sup> is CO<sub>2</sub>H), if chosen, may not be in the ortho-position, R<sup>7</sup> may be H, and R<sup>8</sup> and R<sup>9a</sup> may not be OH. For this reason, the compounds of Blaakmeer, including compound 10, fail to teach or suggest the claimed compounds. Moreover, the Examiner has not provided any reason why one of ordinary skill in the art would have been motivated to modify the Blaakmeer compounds to arrive at the claimed compounds, especially considering the significant structural differences. Indeed, no such rational underpinning exists. See *KSR*, 127 S. Ct. at 1741, 82 U.S.P.Q.2d at 1396 (“[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.”) (citation omitted).

Even assuming for the sake of argument that one of ordinary skill in the art would have been motivated to modify the compounds of Blaakmeer such that they read on the claimed compounds, which Applicants do not concede for the reasons above, nothing in Blaakmeer would have motivated one of ordinary skill in the art to use the modified compounds to treat, diagnose, or prevent the claimed disorders recited in claims 12 and 14-16. Specifically, as the Examiner tacitly acknowledges, Blaakmeer is related to a technical field wholly unrelated to the disorders that the claimed compounds are used to treat, diagnose, or prevent. Indeed, Blaakmeer fails to disclose anything related to the use of pharmaceutical compositions for the treatment of inflammatory disorders. Thus,

not only would one of ordinary skill in the art not have been motivated to modify the compounds of Blaakmeer such that they read on the claimed compounds, that person would also not have been motivated to use the compounds of Blaakmeer to treat the claimed disorders.

Moreover, while Appeldoorn discloses P-selectin inhibiting peptides that might have anti-atherothrombotic effect, Appeldoorn fails to teach or suggest any compound the reads on the claimed compounds. Therefore, there is no rational reason why Appeldoorn would have motivated one of ordinary skill in the art to, first, modify the compounds of Blaakmeer such that they read on the claimed compounds, and, second, use the modified compounds to treat, diagnose, or prevent the claimed disorders.

For these reasons, Applicants respectfully submit that the rejection is in error and should be withdrawn.

**Conclusion**

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration of this application and the timely allowance of the pending claims.

If the Examiner believes a telephone conference could be useful in resolving any outstanding issues, the Examiner is respectfully invited to contact Applicants' undersigned counsel at (202) 292-4060.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 50-4126.

Respectfully submitted,

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